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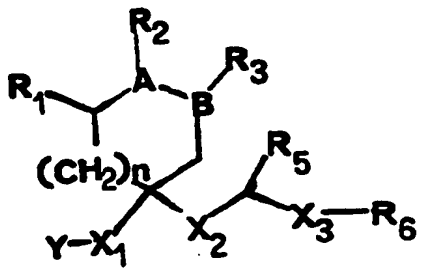
(54) Title: TACHYKININS ANTAGONISTS

(57) Abstract

The present invention refers to tachykinins antagonists of general formula (I), their preparation and pharmaceutical compositions containing them.



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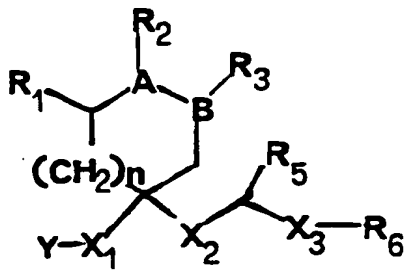
Tachykinins antagonists.

Field of the invention

The present invention refers to tachykinins antagonists of general formula (I)

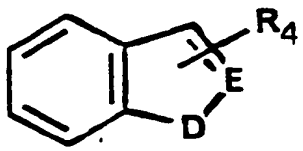


(I)

wherein:

Y is chosen in the group consisting of aryl-, aryl-alkyl-, alkyl-aryl-radical containing from 7 to 12 carbon atoms possibly substituted in the ring with at least one atom chosen in the group consisting of N, S and O and possibly substituted on the ring with one or more substituents independently chosen from halogen, alkyl-radical containing from 1 to 6 carbon atoms possibly substitued with no more than three fluorine atoms (for example trifluoromethyl group), oxyalkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms (for example trifluoromethoxyl group), $-NH_2$, $-NHR_{10}$, $-OR_{10}$, $-N(R_{10})_2$, $-CONHR_{10}$, $-COR_{10}$, $-COOR_{10}$, $-R_{10}COOR_{11}$, $-OR_{10}COOR_{11}$, $-R_{10}COR_{11}$, $-CONHR_{10}$, $-R_{10}CONHR_{11}$, $-NHCOR_{10}$, nitro-radicals wherein R_{10} and R_{11} are hydrogen or an alkyl-radical, linear or branched, containing from 1 to 6 carbon atoms.

or Y is a radical of formula:



wherein D = O, S, CH_2 and N-R_4 wherein R_4 is chosen in the group constitued by hydrogen, an akyl-radical, linear or branched, containing from 1 to 6 carbon atoms, an acyl-radical R_9-CO, wherein R_9 is hydrogen or an akyl-chain containing from 1 to 3 carbon atoms, and wherein E = CH or N, anyone of which can bear suitable substituents;

X_1 and X_2, same or different from each other, are chosen in the group consisting of -$CONR_8$, -NR_8CO-, -CH_2NR_8-, -SO_2NR_8-, wherein R_8 is chosen in the group consisting of hydrogen or an alkyl-chain, linear or modified, containing from 1 to 6 carbon atoms;

X_3 is chosen in the group consisting of -$CONR_7$, -NR_7CO-, -CH_2NR_7-, -SO_2NR_7-, -CN_4-, wherein -CN_4- is a tetrazoline ring and R_7 is chosen in the group consisting of alkyl-, aryl-, aryl-alkyl- or alkyl-aryl-radical with no more than 15 carbon atoms possibly substituted in the ring with at least an atom chosen in the group consisting of N, S and O, possibly substituted on the ring with one or more substituents independently from each other chosen from halogen, alkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms (for example trifluoromethyl group), oxyalkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms (for example trifluoromethoxyl group), -NH_2, -NHR_{10}, -OR_{10}, -$N(R_{10})_2$, -$CONHR_{10}$, -COR_{10}, -$COOR_{10}$, -$R_{10}COOR_{11}$, -$OR_{10}COOR_{11}$, -

$R_{10}COR_{11}$, $-CONHR_{10}$, $-R_{10}CONHR_{11}$, $-NHCOR_{10}$, nitro-radicals, wherein R_{10} and R_{11} are hydrogen or an alkyl-radical, linear or branched, containing from 1 to 6 carbon atoms;

R_1, R_2 and R_3 independently from each other are hydrogen, halogen, OR_{12} wherein R_{12} is chosen in the group consisting of hydrogen, $-CH_2O(CH_2)_2OCH_3$ or $-CH_2O(CH_2)_2OCH_2CH_3$, or are linked two by two to form an epoxide; A and B can be N, S, O or CH; n is a number from 0 to 2;

R_5 and R_6 are chosen, independently from each other, in the group consisting of hydrogen, alkyl-, aryl-, aryl-alkyl or alkyl-aryl-radical containing no more than 15 carbon atoms, possibly substituted in the ring with at least an atom chosen in the group of N, S and O, possibly substituted on the ring with one or more substituents chosen independently from each other from halogen, alkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms (for example trifluoromethyl group), oxyalkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms (for example trifluoromethoxyl group), an $-NH_2$, $-NHR_{11}$, $-OR_{10}$, $-N(R_{10})_2$, $-CONHR_{10}$, $-COR_{10}$, $-COOR_{10}$, $-R_{10}COOR_{11}$, $-OR_{10}COOR_{11}$, $-R_{10}COR_{11}$, $-CONHR_{10}$, $-R_{10}CONHR_{11}$, $-NHCOR_{10}$, nitro-radicals, wherein R_{10} and R_{11} are hydrogen or an alkyl-radical, linear or branched, containing from 1 to 6 carbon atoms.

The invention refers also to the process for their preparation and to pharmaceutical compositions containing them.

State of the art

Tachykinins are a family of at least three peptides, known as Substance P, Neurokinin A (NKA) and Neurokinin B (NKB).

The research in the field of tachykinins antagonists, initially based principally on single or multiple substitutions of the amino acids present in the sequence of peptidic-agonists of Substance P and of the other tachykinins, brought to the discovery of nonapeptides containing one or more units of D-triptophane (Regoli et al. Pharmacol. 28, 301 (1984)). On the other hand the probelms connected with the use as pharmaceuticals products of peptides presenting an high molecular weight (multiplicity of enzymatic hydrolytic attack sites, poor bioavailability, rapid excretion by the liver and kidneys) spurred to search for the smallest peptide fragment still capable of exerting an antagonistic action. These studies brought to the singling out of tri-and di-peptides, suitably substituted, antagonist of Substance P (EP-333 174 and EP- 394 989).

Recently non-peptidic antagonists were reported which do not present the drawbacks of the metabolic instability of peptides (Italian Application MI 92 A 002779):

The compounds of the present invention show antagonism against Substance P, Nurokinin A and Neurokinin B.

Therefore, the above said compounds can be used as pharmaceutical compounds in the treatment and prevention of those disorders wherein the tachykinins Subtance P, Neurokinin A and Neurokinin B play a role as neuromodulators.

The compounds of formula (I) are useful for the treatment of disorders wherein the tachykinins play a patogenic role in particular in the treatment of artritis, asthma, inflammations, tumoral growth, Huntington's disease, neuritis, neuralgia, migraine, hypertension,

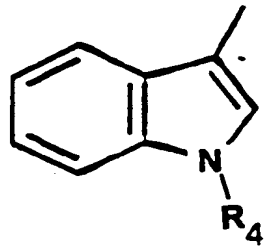
incontinence of urine, urticaria, carcinois syndrome symptoms, influenza and cold, disorders related to the immuno system.

By way of example, reference can be made to patologies of the respiratory system as asthma, allergic rhinitis; ophthalmic system as conjunctivitis; cutaneous system as allergic dermatitis, dermatitis by contact, psoriasis; intestinal system as ulcerative colitis and Chron's disease.

Detailed escription of the invention

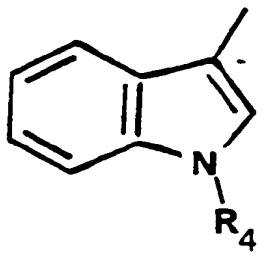
It was surprisingly found, and this is a fundamental characteristic of the present invention, that non-peptidic compounds of general formula (I), as previously defined, show better inhibition of the tachykinins bond to the NK1 receptor and high metabolic stability.

In particular, a preferred group of compounds of the present invention comprises the compounds of formula (I) wherein:

Y= 

wherein X_1 = -CONH-, X_2 = -CONH- and X_3 = -CONCH$_3$- and wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_9, R_{10}, R_{11}, A and B are as above defined.

Particularly preferred are the compounds of formula (I) wherein:

Y= 

wherein X_1 = -CONH-, X_2 = -CONH- and X_3 = -CONCH$_3$-, R_5 = 2-methylnaphthyl and R_6 = benzyl.

In the present invention the alkyl-radical is preferably chosen in the group of: methyl, ethyl, propyl, butyl and pentyl; the alkenyl-radical is chosen between propenyl and butenyl; the aryl-, alkyl-aryl and aryl-alkyl-radical preferably presents an alkyl-radical as above defined while the aryl moiety is preferably pyridine, pirrole, benzofuran, biphenyl, benzene, indole, naphtalene, tetrahydroquinoline, imidazole, tetrahydroindoline, quinoline, thienyl, furan, thiofene, indan, possibly substituted as above defined; cycloalkyl-radical possibly substituted with at least an atom chosen in the group of N, S and O is preferably selected in the group of cyclohexane, cyclopentane, cyclooctane, piperidine, morpholine, piperazine and pyrazine.

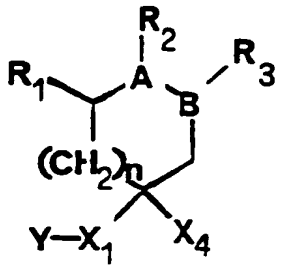
As oxyalkyl-radical is preferred a: methyloxy, ethyloxy, propyloxy, trifluoromethyloxy, while as alkyl radicals methyl and trifluoromethyl are preferred.

Halogen, as used herein, means fluorine, chlorine, bromine and iodine and the groups substituted with no more than three fluorine atoms are preferably tri-substituted.

In view of the asymmetry centres of formula (I), the invention refers to the various diastereoisomers of said formula, in particular the substituent R_5 is preferably in the S-configuration.

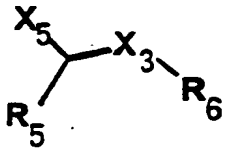
The compounds of general formula (I), as above defined, are prepared according to the following reaction paths and description, wherein, if not otherwise indicated, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{12}, A, B, X_1, X_2, X_3 are as above defined.

a) By condensation, in the presence of a suitable condensing agent, of the intermediate of formula (II), wherein X_4 is COOH or NH_2:



(II)

with the intermediate of formula (III), wherein X_5 is NH_2 when X_4 is COOH, while when X_4 is NH_2, X_5 è COOH:



(III)

The intermediate of general formula (II) is prepared for example according to Scheme 1.

Such Scheme shows the preparation of an intermediate of general formula (IIa) wherein X_1 is $-CH_2-N(Prot_2)-$, by reductive amination of a compound of general formula (V), as above defined, and an aldehyde of general formula Y-CHO with sodium cyanoborohydride or sodium borohydride to give the corresponding intermediate of general formula (VI); this reaction is preferably carried out in acetic acid or alcohol at room temperature, maintaining the pH slightly acid, preferably at pH 4.5. The intermediate (VI) is substituted, giving the intermediate (VII), in order to protect the amino group, and the ester is finally splitted by basic hydrolysis;

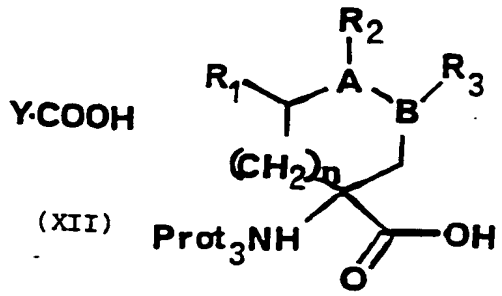
preferably the group introduced is the tert-butyloxycarbonyl-group, and such reaction was carried out with ditert-butylcarbonate in aprotic polar solvents, preferably tetrahydrofuran, at room temperature.

Such intermediate of general formula (III) is prepared, for example, according to Scheme 2.

Scheme 2 describes the preparation of an intermediate of general formula IIIa, wherein X_3 = NR_7CO and R_6, R_5, R_7 are as above defined, HX is an acid chosen in the group: acetic acid, chloridric acid, sulfuric acid, trifluoroacetic acid and the configuration of the carbon atom to which group R_5 is linked is preferably S. Such intermediate is prepared b reaction between the D-amino acid derivative of general formula (VIII, commercialy available or prepared as described in the examples, or by an other synthetic way obvious for the man skilled in the art, and the alkyl-halogenide of general formula R_7-Hal, wherein Hal is chosen in the group of chlorine, iodine or bromine and R_7 is as above described, in the presence of a base, chosen in the group of alkaline- or earth-alkaline-hydrides in an inert, aprotic, polar solvent, for example tetrahydrofuran or dioxane. In particular the reaction is performed at 0°C in tetrahydrofuran using as base sodium-hydride and as alkylating agent methyl iodide. The following reaction with the ammonium salt of hydroxybenzotriazole, carried out in the presence of a suitable condensing agent, gives the corresponding amide (X); the latter by reaction with bis(trifluoracetoxy)iodobenzene produces the gem-diamine derivative (IIIa); such reaction is carried out at room temperature in a water/acetonitrile mixture.

Another synthesis-path, known by the man skilled in the art, is the

sequential condensation on the intermediate of general formula (III), as above defined, of the two residues of general formula (XI) and (XII)



(XII)

(XI)

After the condensation of the first fragment (XI), the elimination of the protecting group $Prot_3$, allows the liberation of the amino-group and the subsequent condensation of fragment (XII), wherein $Prot_3$ is preferably the tert-butyloxycarbonyl-group and the elimination step is an acid lysis, preferably carried out with a saturated solution of hydrochloric acid in organic solvents as ethyle acetate, ethyl ether, dioxane.

b) The reaction by-products are eliminated by evaporating the reaction solvent and teating the residue or a solution thereof in a suitable organic solvent with slightly acid or slightly basic solutions.

c) The crude product obtained from step (b) is purified by chromatography or by cristallization.

The above described condensations can be performed according to the information known in literature for peptide-synthesis.

Excellent product yield and purity, were obtained using, as condensing agent, the benzotriazolyloxytripyrrolidine phosphonium hexafluorophosphate (PyBop). In particular the reaction was carried out

with addition of slight excess of PyBop to a carboxylic component solution, maintained at low temperature, followed by addition of the hydrochloride aminic component and a quantity of tertiary amine of three equivalents in respect to the condensing agent.

An alternative procedure envisages the use, as condensig agent, of 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (WSC.HCl).

For the condensation reaction,which can be preferably carried out at room temperature, the usual polar, aprotic organic solvents chosen in the group of dimethylformamide, dioxane, tetrahydrofuran, methylene chloride, dichloroethane, chloroform are used.

Another object of the present invention are therefore the processes for the preparation of the intermediates of formula (II) and (III) and such intermediates obtained through the above said processes.

The compounds of the present invention can exist in different isomeric configurations. In fact, while the configuration of the carbon atom bound to substituent R_5 is univocally predetermined by the amino acid chosen as starting product, the other starting compounds can be a mixture of enantiomers difficult to separate. It follows that the present compounds can be obtained as diastereoisomers mixtures. Said mixtures can be easily resolved by chromatography. In any case compounds of formula (I) can be used both in optically active form and in the form of isomeric mixtures.

For their therapeutical use the compounds according to the present invention can be administered parenterally, intranasaly, orally or sublingually. The formulations containing the new compounds can be prepared, according to known techniques, combining the active principle with an inert carrier and possibly with the conventional additives

suitably chosen. In view of the oral or sublingual use the present compounds can be administered as tablets, pellets, drops, elixir, ecc., prepared with the conventional carriers/excipients as starch, sugars, water, alcohol ecc. and possibly comprising aromatizing agents, stabilizers, preservatives, lubricants ecc. For parenteral or intranasal administration the preferred carrier is sterilized water for injection. Additives can be added according to the known art.

The therapeutically effective daily dosage can vary according to the subject under treatment (weight, age, disease gravity) and to the administration route. Generally it can be said that the present compounds are active when subministered in a daily dosage of 0.005 to 10 mg/Kg. The pharmaceutical compositions according to the present invention will contain the active product in a suitable quantity in order to allow a correct daily dosage in the above said range, normally by 1 - 3 administrations per day.

The following example is given for better illustrating the invention.

EXAMPLE

N^{α}[N-(1(H)indol-3-yl-carbonyl)-1-amino-cyclohexan-carbonyl]-L-2-naphthylalanine-N-methyl-N-benzylamide [I3c-1-Ac^{6}c-L-2Nal-NMeBz]

For the sake of simplicity the following abreviations were also used: 1-Ac^{6}c, for the 1-amino-cyclohexancarboxylic-acid; I3c, for the 1(H)indol-3-yl-carbonyl-residue; the indications normally used for the peptide synthesis.

1a) To an amino-cyclohexanecarboxylic-acid (1.4 g) in 14 ml of NaOH 2N, cooled at 0°C under vigorous stirring in nitrogen current, a solution of di-tert-butyl-dicarbonate (9.1 g) in 14 ml of isopropanole was added. The

solution was left under stirring at room temperature for 16 hours. The isopropanole was evaporated in vacuo and the aqueous solution was extracted with ethyl ether (3 x 50 ml). The aqueous phase was acidified to pH 3 with HCl 1N and extracted with ethyle acetate (3 x 50 ml). The organic solution was washed with a solution saturate in NaCl (3 x 50 ml), dried on Na_2SO_4 and the solvent was eliminated obtaining 309 mg of N^{α}(tert-butyloxy-carbonyl)-1-aminocyclohexanecarboxylic acid (Boc-1-Ac^6c-OH) (yield 47%). TLC [chloroform/methanole 9:1 v/v (CM)] = 0.36.

1b) to a solution of N^{α}(tert-butyloxy-carbonyl)-L-2-napthylalanine (500 mg) in 7 ml of anhydrous DCM, at 0°C under vigorous stirring in nitrogen current, N,N-methylbenzylamine (0.25 ml), N-hydroxybenzotriazolyl-tripyrrolidine phosphonium hexafluorophasphate (PyBop) (0.998 g) and finally, slowly, DiPEA (0.63 ml) are added. The solution is left under stirring at 0°C for 30' and at room temperature for 16 hours. The solvent is eliminated by evaporation in vacuo and the residue is collected with EtOAc (50 ml). The organic solution is extracted with an aqueous solution of $NaHCO_3$ (3 x 50 ml), therefater with an aqueous solution saturated in NaCl (3 x 50 ml), with an aqueous solution of HCl 0.1 N (3 x 50 ml) and finally again with an aqueous solution saturated in NaCl (3 x 50 ml). The organic phase is dried on Na_2SO_4 and the solvent is eliminated giving a slightly yellow oil which is purified by chromatography on silica using as eluent hexane/ethyle acetate 70:30 (v/v) giving 478 mg of N^{α}(tert-butyloxycarbonyl)-L-2-naphthylalanine-N-methyl-N-benzyl amide (yield 71%).

TLC [chloroform/methyl alcohol 95:5 v/v] = 0.85.

for the HPLC a Phase Sep. Spherisorb ODS-2^R 5m 46 x 250 mm was used and

as eluents:

A = 0.1 trifluoroacetic acid in acetonitrile

B = 0.1 trifluoroacetic acid in water

linear gradient of 20% A to 80% A over 25 min; isocratic conditions at 80% of A for 10 min, flow 1 ml/min; determination by UV at 230 nm.

Analytical HPLC shows a single peak at T_R = 28.55 min.

1c) A suspension of the product obtained in the previous step (1b) (0.474 g) in 9 ml of a solution of EtOAc saturated of HCl (about 2N) is left under stirring at room temperature for 30 min. The solvent is eliminated under a slight nitrogen current and the residue is repeatedly suspended in ethyl ethere (4 x 30 ml), the solvent is eliminated giving 0.400 mg of L-2-naphthylalanine-N-methyl-N-benzyl amide hydrochloride (yield 99%).

TLC [chloroform/methyl alcohol 95:5 v/v): Rf = 0.15.

Analytical HPLC in the same conditions given for step (1b) shows a single peak, large, at T_R = 24.44 min.

1d) To a solution of the compound of step (1a) (0.170 g) in DCM (2 ml) and DMF (0.2 ml), at 0°C under vigorous stirring in nitrogen current, 0.11 g of HOBt and 0.16 g of WSC.HCl are added. The solution is left under stirring at 0°C for 30' and therefater 0.25 g of the compound obtained in step (1c) and 0.28 ml of diisopropylethylamine are added. After 16 hours stirring at room temperature, the solvent was eliminated by evaporation in vacuo and recollected with ethyl acetate. The organic solution is extracted with an aqueous solution of $NaHCO_3$ at 5% (3 x 50 ml), thereafter with an aqueous solution saturated in NaCl (3 x 50 ml), then with an aqueous solution of HCl 0.1 N (3 x 50 ml) and finally again with an aqueous solution saturated in NaCl (3 x 50 ml). The organic phase

is dried on Na_2SO_4 and the solvent is eliminated. The residue is solubilized in 20 ml of an ethyl acetate solution saturated with hydrochloric acid (about 2N). After 1 hour stirring at room temperature, the solvent is evaporated under nitrogen current, the residue is recollected twice with absolute etanole and the solvent is eliminated. The compound is cristallized from carbon tetrachloride giving 320 mg of N^{α}(1-aminocyclohexylcarbonyl)-L-2-naphthylalanine-N-metil-N-benzyl-amine hydrochloride (yield 95%).

TLC [Chloroform/methyl alcohol/acetic acid 85:10:5 v/v): Rf = 0.43.

Analytical HPLC in the same conditions as in step (1b) shows a single peak, large, at T_R = 28.16 min.

1e) A suspension of 3-indolyl-carboxylyc acid (0,125 g) in 1.6 ml of a 1 M solution of oxalyl chloride in benzene, cooled at 0°C, is kept under stirring in nitrogen current for 1 hour. After addition of two drops of DMF, the solution, now clear and slightly yellow, is left under stirring at room temperature for another hour. The solvent was eliminated by evaporation under reduced pressure and the residue was recollected with 1 ml of DCM, the resulting solution was added to a solution of the compound obtained in step (1d) (40 mg) and diisopropylethylamine (0.23 ml) in 0.5 ml DCM. The solution was left under stirring at room temperature for 24 hours. After elimination of the solvent under reduced pression, the residue was recollected in ethyl acetate (5 ml) and extracted with an aqueous solution of 5% $NaHCO_3$ (3 x 50 ml), then with an aqueous solution saturated in NaCl (3 x 50 ml), with an aqueous solution of HCl 0.1 N (3 x 50 ml) and finally with an aqueous solution saturated of NaCl (3 x 50 ml). The organic phase is dried over Na_2SO_4 and the solvent is

eliminated. The product is isolated by reversed-phase chromatography on a Hibar Merck column filled with Lichrosorb RP-18^{R} (7 m), eluting with isocratic at 65% of A (eluent of step ib), flow 8 ml/min. The fractions corresponding to the product peak were pooled, concentrated to small volume under reduced pressure and repeatedly free-dried giving 9 mg of N^{α}[N-(1(H)indol-3-yl-carbonyl)-1-amino-cyclohexancarbonyl]-L-2-naphthylalanine-N-methyl-N-benzyl amide.

Analytical HPLC, in the same conditions described for step (1b) shows a single peak at T_R = 27.71 min.

Operating as above described the following compounds were obtained:

i) 1-N-[N(1(H)indol-3-yl-carbonyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2-phenylethane

ii) 1-[N(1(H)indol-3-yl-carbonyl)-1-amino-cyclohexancarbonyl]-amino-1[N-(2-phenylacetyl)amino]-2-(2-naphthyl)ethane

iii) 1-N-[N(benzoyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

iv) 1-N-[N(4-methyl-benzoyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

v) 1-N-[N(4-metoxy-benzoyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

vi) 1-N-[N(4-chloro-benzoyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

vii) 1-N-[N(3,4-chloro-benzoyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

viii) 1-N-[N(1(methyl)indol-3-yl-carbonyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

ix) 1-N-[N(1(H)indol-3-yl-methyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

x) 1-N-[N(1(methyl)indol-3-yl-carbonyl)-N-methyl-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

xi) 1-N-[N(1(H)indol-3-yl-carbonyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(p-methoxy)phenylethane

xii) N-[N(1(methyl)indol-3-yl-carbonyl)-N-methyl-1-amino-cyclohexancarbonyl]-2 naphthylalanine-N-methyl-N-benzylamide

xiii) N-[N(1(methyl)indol-3-yl-carbonyl)-N-methyl-1-amino-cyclohexancarbonyl]-2 naphthylalanine-N-methyl-N-benzylamide

xiv) 1-N-[N(1(H)indol-3-yl-carbonyl)-1-amino-cis-4-hydroxy-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]-amino-2-phenylethane

xv) 1-[N-(1(H)indol-3-yl-carbonyl)-1-amino-trans-4-hydroxy-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]-amino-2-(2-naphthyl)ethane

xvi) 1-N-[N(1(H)indol-3-yl-carbonyl)-1-amino-cis-4-methoxyethoxymethoxyl-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]-amino-2-phenylethane

xvii) 1-[N(1(H)indol-3-yl-carbonyl)-1-amino-trans-4-methoxyethoxymethoxyl-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]-2(2-naphthyl)ethane

xviii) N-[N(1(H)indol-3-yl-carbonyl)-1-amino-cis-4-hydroxy-cyclohexancarbonyl]-2-naphthylalanine-N-methyl-N-benzylamide

xix) N-[N(1(H)indol-3-yl-carbonyl)-1-amino-trans-4-hydroxy-

cyclohexancarbonyl]-2-naphthylalanine-N-methyl-N-benzylamide

xx) N-[N(1(H)indol-3-yl-carbonyl)-1-amino-cis-4-methoxyethoxymethoxyl-cyclohexancarbonyl]-phenylalanine-N-methyl-N-benzylamide

xxi) N-[N(1(H)indol-3-yl-carbonyl)-1-amino-trans-4-methoxyethoxymethoxyl-cyclohexancarbonyl]-phenylalanine-N-methyl-N-benzylamide

xxii) 1-[N(1(H)indol-3-yl-carbonyl)-1-amino-4-dimethoxy-cyclohexancarbonyl]-amino-1-[N(methyl)-N(2-phenylacetyl)]-amino-2-(2-naphthyl)ethane

xxiii) N-[N(1(H)indol-3-yl-carbonyl)-1-amino-4-dimethoxy-cyclohexancarbonyl]-2-naphthylalanine-N-methyl-N-benzylamide

xxiv) 1-[N(1(H)indol-3-yl-carbonyl)-1-amino-4-di(methoxyethoxyethoxy)-cyclohexancarbonyl]-amino-1-[N(methyl)-N(2-phenylacetyl)]-amino-2-(2-naphthyl)ethane

xxv) N-[N(1(H)indol-3-yl-carbonyl)-1-amino-4-di(methoxyethoxymethoxy)-cyclohexancarbonyl]-2-naphthylalanine-N-methyl-N-benzylamide

xxvi) 1-[N(1(H)indol-3-yl-carbonyl)-4-amino-tetrahydropyranyl-4-carbonyl]-amino-1[N(methyl)-N(2-phenylacetyl)]-amino-2-(2-naphthyl)ethane

xxvii) N-[N(1(H)indol-3-yl-carbonyl)-4-amino-tetrahydropyranyl-4-carbonyl]-2-naphthylalanine-N-methyl-N-benzylamide

xxviii) 1-[N(1(H)indol-3-yl-carbonyl)-4-amino-piperidin-4-carbonyl]-amino-1[N(methyl)-N(2-phenylacetyl)]-amino-2-(2-naphthyl)ethane

xxix) N-[N(1(H)indol-3-yl-carbonyl)-4-amino-piperidin-4-carbonyl]-2-naphthylalanine-N-methyl-N-benzylamide

xxx) 1-[N(1(H)indol-3-yl-carbonyl)-4-amino-1-dimethyl-piperidin-4-carbonyl]-amino-1-[N(methyl)-N(2-phenylacetyl)]-amino-2-(2-

naphthyl)ethane

xxxi) N-[N(1(H)indol-3-yl-carbonyl)-4-amino-1-dimethylpiperidin-4-carbonyl]-2-naphthylalanine-N-methyl-N-benzylamide

The evaluetion of the antagonist acivity of NK1 receptors was performed with binding and functional tests.

[^{3}H]SP binding assay in IM9 Cell Line.

The assay was carried out on intact cells as described by Payan et al. (1984). The cells were washed with buffer A at pH 7.5 containing (in mM) Tris-HCl 50, NaCl 150 and 0.02% BSA, thereafter were resuspended in a dosage buffer (buffer A added with protease inhibitors), concentration $x 10^7$ cells/ml. The cells were incubated with [^{3}H]SP in a final volume of 0.5 ml for 60' at room temperature. The non-specific binding was calculated in the presence of 10 mM of non-radioactive SP. The dosage mixture was poured in test tubes for microcentrifugation which were preadsorbed in a solution of BSA 0.5% for at least 3 hours. [^{3}H]SP, free and binded, was separated by cell sedimentation with a microcentrifuge (6 min at 12000 g); the supernatant was removed by aspiration. For competitive tests, the cells IM9 were incubated in triplicate with 0.3 nM of [^{3}H]SP (average value of Kd calculated in saturation experiments) and the competitive ligands were added at six different concentrations (with dilution 1:10 in the dosage buffer) in order to obtain a complete competition curve. The affinity was measured as pKi.

Measurement of pA2 in isolated guinea pig ileum

Male guinea pigs weighing 300-350 g were sacrificed. A ring of ileum (about 3 mm width) deprived of the plexus myentericus, was excised and placed in oxygenated Krebs solution containing 10 µM indomethacin. The

sample is mounted on steel hooks and connected with an isotonic transductor (charge 5 mN). After 90 minutes equilibration a cumulative curve for the agonist ([Sar^9]Substance P sulphone) was determined. After two or more reproducible curves for the agonist had been obtained, the compound to be tested was added to the bath and a new curve for the agonist was determined in its presence. pA2 values were calculated by using the constrained Schild plot method.

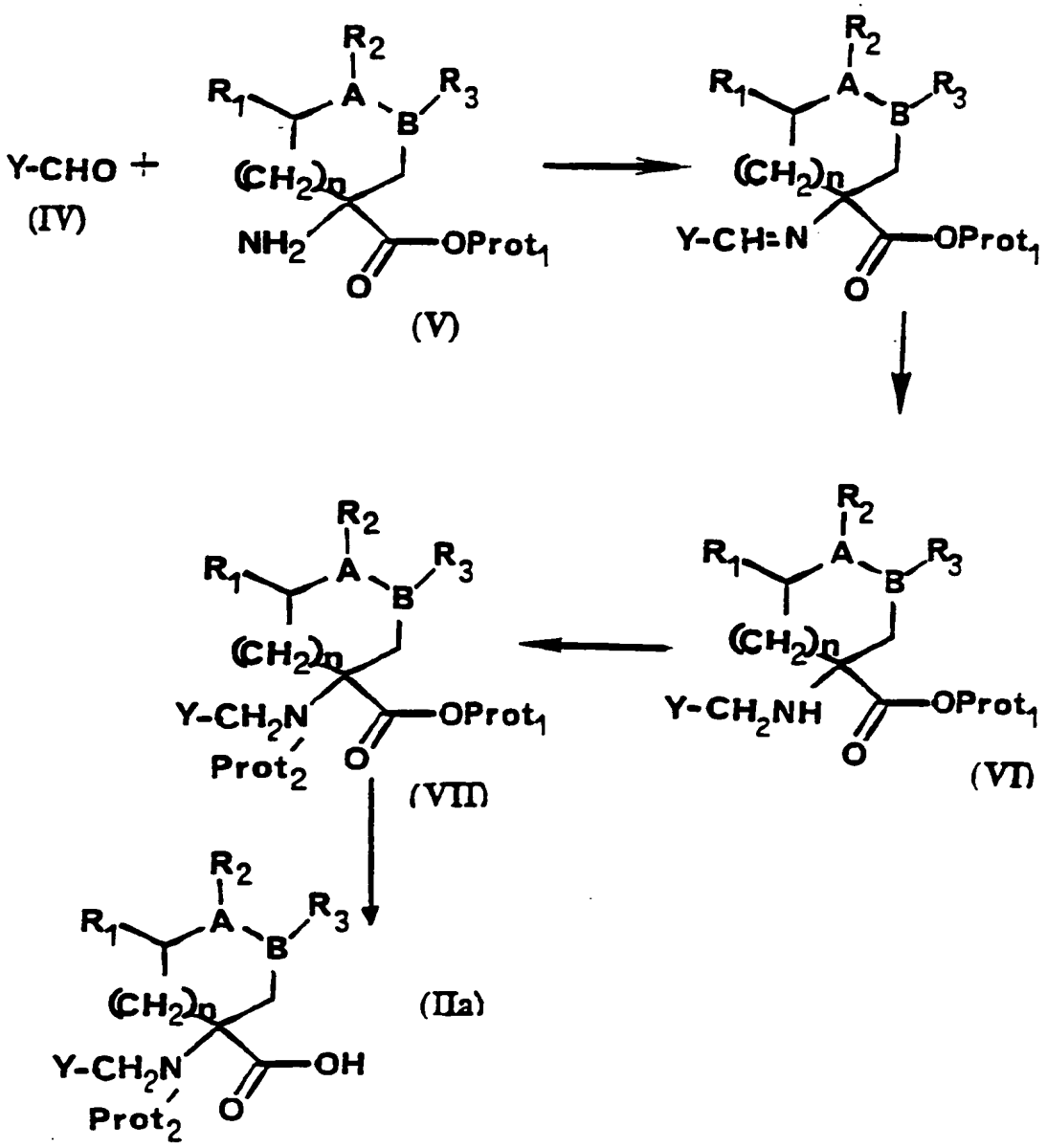
The data in Table I were obtained for compounds of general formula (I).

Table I

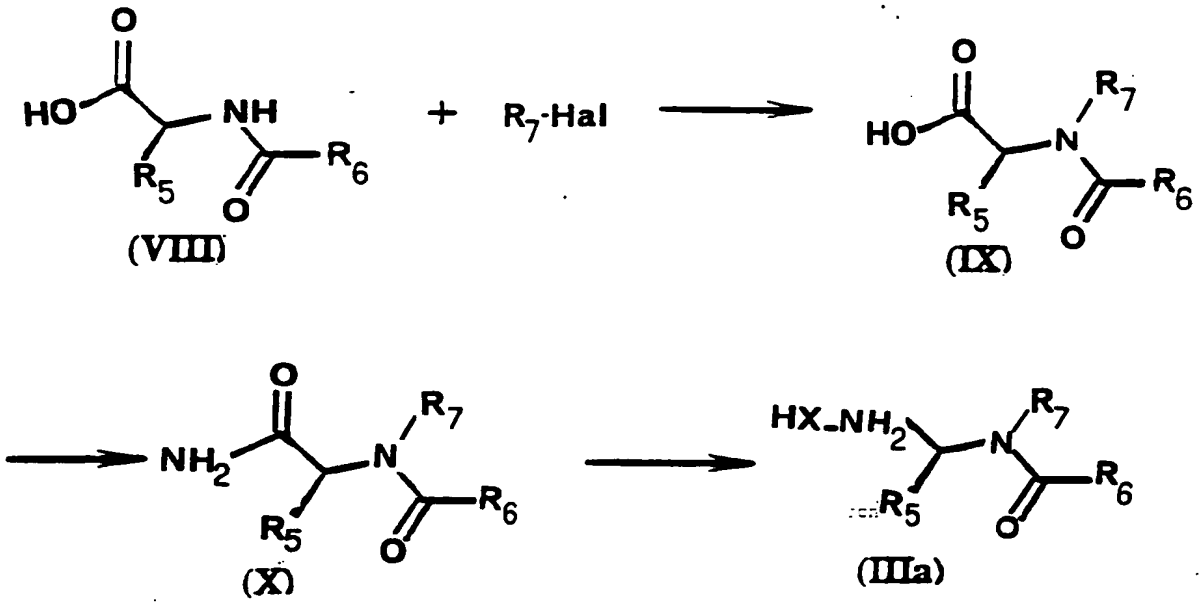
Antagonism of Substance P

Compound of Ex. 1	100% inhibition at 1μM

SCHEME 1

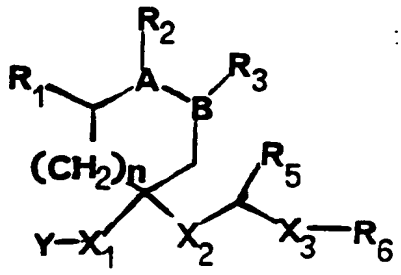


SCHEME 2



Claims

1. Tachykinins antagonist of general formula (I)

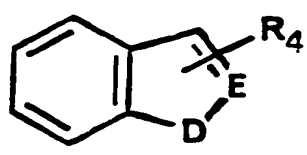


(I)

wherein:

Y is chosen in the group consisting of aryl-, aryl-alkyl-, alkyl-aryl- radical containing from 7 to 12 carbon atoms possibly substituted in the ring with at least one atom chosen in the group consisting of N, S and O and possibly substituted on the ring with one or more substituents independently chosen from halogen, alkyl-radical containing from 1 to 6 carbon atoms possibly substitued with no more than three fluorine atoms, oxyalkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms, $-NH_2$, $-NHR_{10}$, $-OR_{10}$, $-N(R_{10})_2$, $-CONHR_{10}$, $-COR_{10}$, $-COOR_{10}$, $-R_{10}COOR_{11}$, $-OR_{10}COOR_{11}$, $-R_{10}COR_{11}$, $-CONHR_{10}$, $-R_{10}CONHR_{11}$, $-NHCOR_{10}$, nitro-radicals wherein R_{10} and R_{11} are hydrogen or an alkyl-radical, linear or branched, containing from 1 to 6 carbon atoms,

or Y is a radical of formula:



wherein D = O, S, CH_2 and N-R_4 wherein R_4 is chosen in the group constitued by hydrogen, an akyl-radical, linear or branched, containing from 1 to 6 carbon atoms, an acyl-radical R_9-CO, wherein R_9 is hydrogen or an akyl-chain containing from 1 to 3 carbon atoms, and wherein E = CH or N, anyone of which can bear suitable substituents;

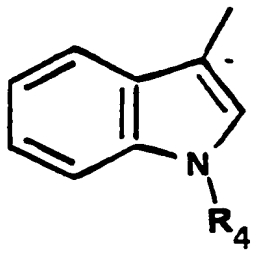
X_1 and X_2, same or different from each other, are chosen in the group consisting of -$CONR_8$, -NR_8CO-, -CH_2NR_8-, -SO_2NR_8-, wherein R_8 is chosen in the group consisting of hydrogen or an alkyl-chain, linear or modified, containing from 1 to 6 carbon atoms;

X_3 is chosen in the group consisting of -$CONR_7$, -NR_7CO-, -CH_2NR_7-, -SO_2NR_7-, -CN_4-, wherein -CN_4- is a tetrazoline ring and R_7 is chosen in the group consisting of alkyl-, aryl-, aryl-alkyl- or alkyl-aryl-radical with no more than 15 carbon atoms possibly substituted in the ring with at least an atom chosen in the group consisting of N, S and O, possibly substituted on the ring with one or more substituents independently from each other chosen from halogen, alkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms, oxyalkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms, -NH_2, -NHR_{10}, -OR_{10}, -$N(R_{10})_2$, -$CONHR_{10}$, -COR_{10}, -$COOR_{10}$, -$R_{10}COOR_{11}$, -$OR_{10}COOR_{11}$, -$R_{10}COR_{11}$, -$CONHR_{10}$, -$R_{10}CONHR_{11}$, -$NHCOR_{10}$, nitro-radicals, wherein R_{10} and R_{11} are hydrogen or an alkyl-radical, linear or branched, containing from 1 to 6 carbon atoms;

R_1, R_2 and R_3 independently from each other are hydrogen, halogen, OR_{12} wherein R_{12} is chosen in the group consisting of hydrogen, -$CH_2O(CH_2)_2OCH_3$ or -$CH_2O(CH_2)_2OCH_2CH_3$, or are linked two by two to form

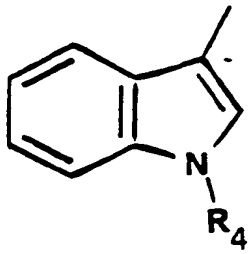
an epoxide; A and B can be N, S, O or CH; n is a number from 0 to 2; R_5 and R_6 are chosen, independently from each other, in the group consisting of hydrogen, alkyl-, aryl-, aryl-alkyl or alkyl-aryl-radical containing no more than 15 carbon atoms, possibly substituted in the ring with at least an atom chosen in the group of N, S and O, possibly substituted on the ring with one or more substituents chosen independently from each other from halogen, alkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms, oxyalkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms, an $-NH_2$, $-NHR_{11}$, $-OR_{10}$, $-N(R_{10})_2$, $-CONHR_{10}$, $-COR_{10}$, $-COOR_{10}$, $-R_{10}COOR_{11}$, $-OR_{10}COOR_{11}$, $-R_{10}COR_{11}$, $-CONHR_{10}$, $-R_{10}CONHR_{11}$, $-NHCOR_{10}$, nitro-radicals, wherein R_{10} and R_{11} are hydrogen or an alkyl-radical, linear or branched, containing from 1 to 6 carbon atoms.

2. Compound according to claim 1, wherein:

Y= 

wherein X_1 = -CONH-, X_2 = -CONH- and X_3 = $-CONCH_3-$ and wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_9, R_{10}, R_{11}, A and B are as above defined.

3. Compound according to claim 2, wherein:

Y= 

wherein X_1 = -CONH-, X_2 = -CONH- and X_3 = -CONCH$_3$-, R_5 = 2-methylnaphthyl and R_6 = benzyl.

4. Compound according to claim 1 wherein the alkyl-radical is preferably chosen in the group of: methyl, ethyl, propyl, butyl and pentyl; the alkenyl-radical is chosen between propenyl and butenyl; the aryl-, alkyl-aryl and aryl-alkyl-radical preferably presents an alkyl-radical as above defined while the aryl moiety is preferably pyridine, pirrole, benzofuran, biphenyl, benzene, indole, naphtene, tetrahydroquinoline, imidazole, tetrahydroindoline, quinoline, thienyl, furan, thiofene, indan, possibly substituted as abobe defined; cycloalkyl-radical possibly substituted with at least an atom chosen in the group of N, S and O is preferably selected in the group of cyclohexane, cyclopentane, cyclooctane, piperidine, morpholine, piperazine and pyrazine. The term halogen is chlorine, fluorine, bromine and iodine.

5. Compound of general formula (I) according to claim 1 as herein defined:

i) 1-N-[N(1(H)indol-3-yl-carbonyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2-phenylethane

ii) 1-[N(1(H)indol-3-yl-carbonyl)-1-amino-cyclohexancarbonyl]-amino-1[N-(2-phenylacetyl)amino]-2-(2-naphthyl)ethane

iii) 1-N-[N(benzoyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-

phenylacetyl)]amino-2(2-naphthyl)ethane

iv) 1-N-[N(4-methyl-benzoyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

v) 1-N-[N(4-metoxy-benzoyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

vi) 1-N-[N(4-chloro-benzoyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

vii) 1-N-[N(3,4-chloro-benzoyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

viii) 1-N-[N(1(methyl)indol-3-yl-carbonyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

ix) 1-N-[N(1(H)indol-3-yl-methyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

x) 1-N-[N(1(methyl)indol-3-yl-carbonyl)-N-methyl-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(2-naphthyl)ethane

xi) 1-N-[N(1(H)indol-3-yl-carbonyl)-1-amino-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]amino-2(p-methoxy)phenylethane

xii) N-[N(1(methyl)indol-3-yl-carbonyl)-N-methyl-1-amino-cyclohexancarbonyl]-2 naphthylalanine-N-methyl-N-benzylamide

xiii) N-[N(1(methyl)indol-3-yl-carbonyl)-N-methyl-1-amino-cyclohexancarbonyl]-2 naphthylalanine-N-methyl-N-benzylamide

xiv) 1-N-[N(1(H)indol-3-yl-carbonyl)-1-amino-cis-4-hydroxy-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]-amino-2-phenylethane

xv) 1-[N-(1(H)indol-3-yl-carbonyl)-1-amino-trans-4-hydroxy-

cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]-amino-2-(2-naphthyl)ethane

xvi) 1-N-[N(1(H)indol-3-yl-carbonyl)-1-amino-cis-4-methoxyethoxymethoxyl-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]-amino-2-phenylethane

xvii) 1-[N(1(H)indol-3-yl-carbonyl)-1-amino-trans-4-methoxyethoxymethoxyl-cyclohexancarbonyl]-amino-1-[N(methyl)N(2-phenylacetyl)]-2(2-naphthyl)ethane

xviii) N-[N(1(H)indol-3-yl-carbonyl)-1-amino-cis-4-hydroxy-cyclohexancarbonyl]-2-naphthylalanine-N-methyl-N-benzylamide

xix) N-[N(1(H)indol-3-yl-carbonyl)-1-amino-trans-4-hydroxy-cyclohexancarbonyl]-2-naphthylalanine-N-methyl-N-benzylamide

xx) N-[N(1(H)indol-3-yl-carbonyl)-1-amino-cis-4-methoxyethoxymethoxyl-cyclohexancarbonyl]-phenylalanine-N-methyl-N-benzylamide

xxi) N-[N(1(H)indol-3-yl-carbonyl)-1-amino-trans-4-methoxyethoxymethoxyl-cyclohexancarbonyl]-phenylalanine-N-methyl-N-benzylamide

xxii) 1-[N(1(H)indol-3-yl-carbonyl)-1-amino-4-dimethoxy-cyclohexancarbonyl]-amino-1-[N(methyl)-N(2-phenylacetyl)]-amino-2-(2-naphthyl)ethane

xxiii) N-[N(1(H)indol-3-yl-carbonyl)-1-amino-4-dimethoxy-cyclohexancarbonyl]-2-naphthylalanine-N-methyl-N-benzylamide

xxiv) 1-[N(1(H)indol-3-yl-carbonyl)-1-amino-4-di(methoxyethoxyethoxy)-cyclohexancarbonyl]-amino-1-[N(methyl)-N(2-phenylacetyl)]-amino-2-(2-naphthyl)ethane

xxv) N-[N(1(H)indol-3-yl-carbonyl)-1-amino-4-di(methoxyethoxymethoxy)-

cyclohexancarbonyl]-2-naphthylalanine-N-methyl-N-benzylamide

xxvi) 1-[N(1(H)indol-3-yl-carbonyl)-4-amino-tetrahydropyranyl-4-carbonyl]-amino-1[N(methyl)-N(2-phenylacetyl)]-amino-2-(2-naphthyl)ethane

xxvii) N-[N(1(H)indol-3-yl-carbonyl)-4-amino-tetrahydropyranyl-4-carbonyl]-2-naphthylalanine-N-methyl-N-benzylamide

xxviii) 1-[N(1(H)indol-3-yl-carbonyl)-4-amino-piperidin-4-carbonyl]-amino-1[N(methyl)-N(2-phenylacetyl)]-amino-2-(2-naphthyl)ethane

xxix) N-[N(1(H)indol-3-yl-carbonyl)-4-amino-piperidin-4-carbonyl]-2-naphthylalanine-N-methyl-N-benzylamide

xxx) 1-[N(1(H)indol-3-yl-carbonyl)-4-amino-1-dimethyl-piperidin-4-carbonyl]-amino-1-[N(methyl)-N(2-phenylacetyl)]-amino-2-(2-naphthyl)ethane

xxxi) N-[N(1(H)indol-3-yl-carbonyl)-4-amino-1-dimethylpiperidin-4-carbonyl]-2-naphthylalanine-N-methyl-N-benzylamide.

6. Pharmaceutical composition comprising as active principle a therapeutically effective amount of compound of formula (I) according to claim 1.

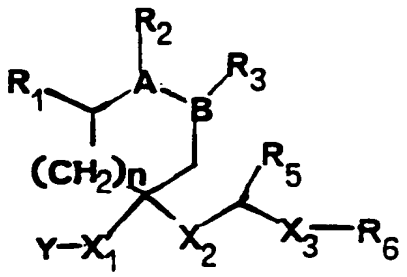
7. Pharmaceutical composition comprising as active principle a therapeutically effective amount of compound of formula (I) according to claim 2.

8. Pharmaceutical composition comprising as active principle a therapeutically effective amount of compound of formula (I) according to claim 3.

9. Use of compounds of formula (I) according to claims 1, 2, 3, 4 as active principle for the preparation of pharmaceutical compositions.

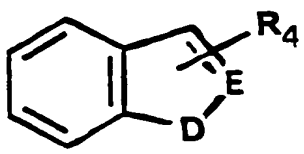
10. Process for the preparation of compounds of general formula (I):

wherein:



Y is chosen in the group consisting of aryl-, aryl-alkyl-, alkyl-aryl- radical containing from 7 to 12 carbon atoms possibly substituted in the ring with at least one atom chosen in the group consisting of N, S and O and possibly substituted on the ring with one or more substituents independently chosen from halogen, alkyl-radical containing from 1 to 6 carbon atoms possibly substitued with no more than three fluorine atoms, oxyalkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms, $-NH_2$, $-NHR_{10}$, $-OR_{10}$, $-N(R_{10})_2$, $-CONHR_{10}$, $-COR_{10}$, $-COOR_{10}$, $-R_{10}COOR_{11}$, $-OR_{10}COOR_{11}$, $-R_{10}COR_{11}$, $-CONHR_{10}$, $-R_{10}CONHR_{11}$, $-NHCOR_{10}$, nitro-radicals wherein R_{10} and R_{11} are hydrogen or an alkyl-radical, linear or branched, containing from 1 to 6 carbon atoms.

or Y is a radical of formula:



wherein D = O, S, CH_2 and N-R_4 wherein R_4 is chosen in the group constitued by hydrogen, an akyl-radical, linear or branched, containing from 1 to 6 carbon atoms, an acyl-radical R_9-CO, wherein R_9 is hydrogen or an akyl-chain containing from 1 to 3 carbon atoms, and wherein E = CH or N, anyone of which can bear suitable substituents;

X_1 and X_2, same or different from each other, are chosen in the group consisting of -$CONR_8$, -NR_8CO-, -CH_2NR_8-, -SO_2NR_8-, wherein R_8 is chosen in the group consisting of hydrogen or an alkyl-chain, linear or modified, containing from 1 to 6 carbon atoms;

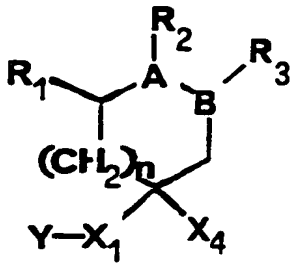
X_3 is chosen in the group consisting of -$CONR_7$, -NR_7CO-, -CH_2NR_7-, -SO_2NR_7-, -CN_4-, wherein -CN_4- is a tetrazoline ring and R_7 is chosen in the group consisting of alkyl-, aryl-, aryl-alkyl- or alkyl-aryl-radical with no more than 15 carbon atoms possibly substituted in the ring with at least an atom chosen in the group consisting of N, S and O, possibly substituted on the ring with one or more substituents independently from each other chosen from halogen, alkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms, oxyalkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms, -NH_2, -NHR_{10}, -OR_{10}, -$N(R_{10})_2$, -$CONHR_{10}$, -COR_{10}, -$COOR_{10}$, -$R_{10}COOR_{11}$, -$OR_{10}COOR_{11}$, -$R_{10}COR_{11}$, -$CONHR_{10}$, -$R_{10}CONHR_{11}$, -$NHCOR_{10}$, nitro-radicals, wherein R_{10} and R_{11} are hydrogen or an alkyl-radical, linear or branched, containing from 1 to 6 carbon atoms;

R_1, R_2 and R_3 independently from each other are hydrogen, halogen, OR_{12} wherein R_{12} is chosen in the group consisting of hydrogen, -$CH_2O(CH_2)_2OCH_3$ or -$CH_2O(CH_2)_2OCH_2CH_3$, or are linked two by two to form

an epoxide; A and B can be N, S, O or CH; n is a number from 0 to 2; R_5 and R_6 are chosen, independently from each other, in the group consisting of hydrogen, alkyl-, aryl-, aryl-alkyl or alkyl-aryl-radical containing no more than 15 carbon atoms, possibly substituted in the ring with at least an atom chosen in the group of N, S and O, possibly substituted on the ring with one or more substituents chosen independently from each other from halogen, alkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms, oxyalkyl-radical containing from 1 to 6 carbon atoms, possibly substituted with no more than three fluorine atoms, an $-NH_2$, $-NHR_{11}$, $-OR_{10}$, $-N(R_{10})_2$, $-CONHR_{10}$, $-COR_{10}$, $-COOR_{10}$, $-R_{10}COOR_{11}$, $-OR_{10}COOR_{11}$, $-R_{10}COR_{11}$, $-CONHR_{10}$, $-R_{10}CONHR_{11}$, $-NHCOR_{10}$, nitro-radicals, wherein R_{10} and R_{11} are hydrogen or an alkyl-radical, linear or branched, containing from 1 to 6 carbon atoms;

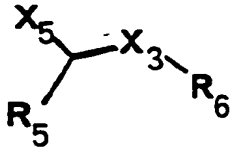
according to the following steps:

a) preparation of the intermediate of formula (II):



(II)

and of the intermediate of formula (III) wherein X_5 is NH_2 when X_4 is COOH while X_5 is COOH when X_4 is NH_2:



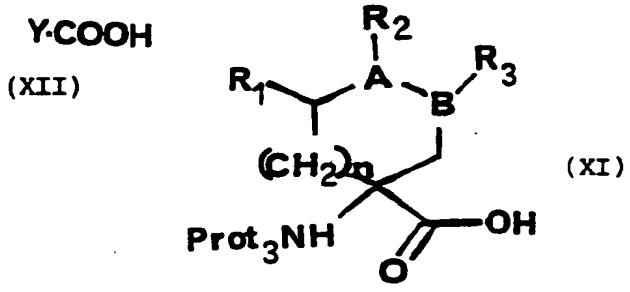
(III)

and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{12}, A, B, Y, X_1, X_2, X_3, are as above defined in claim 1;

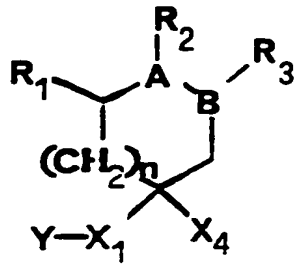
b) condensation, in the presence of a suitable condensing agent of the two above said intermediates;

c) isolation and purification of the product from step (b) by chromatography.

11. Process for the preparation of a compound of formula (I) according to claim 10 by sequential condensation on the intermediate of general formula (III), as above described wherein X_5 is NH_2, of the two redidues of general formula (XI) and (XII)



12. Compound of general formula (II)



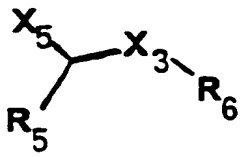
(II)

wherein R_1, R_2, R_3, R_5, R_6, A, B, X_1, X_2, X_3, X_4, X_5 are as defined in

claim 1.

13. compound of general formula (III)

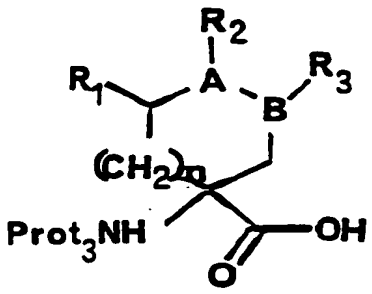
(III)



wherein R_1, R_2, R_3, R_5, R_6, A, B, X_1, X_2, X_3, X_4, X_5 are as defined in claim 1.

14. Compound of general formula (XI)

(XI)



wherein R_1, R_2, R_3, R_5, R_6, A, B, X_1, X_2, X_3, X_4, X_5 are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/EP 95/00193

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/42 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 443 132 (FUJISAWA PHARMACEUTICAL CO.,LTD.) 28 August 1991 see claims ---	1,6
A	EP,A,0 394 989 (FUJISAWA PHARMACEUTICAL CO.,LTD.) 31 October 1990 see claims ---	1,6
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 36,no. 16, 6 August 1993 pages 2266-2278, DAIJIRO HAGIWARA ET AL. 'Studies on neurokinin antagonists. 3....' * page 2267 * ---	1,6
P,A	WO,A,94 13694 (A. MENARINI INDUSTRIE FARMACEUTICHE RIUNITE S.R.L.) 23 June 1994 see claims -----	1,6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

- 1

Date of the actual completion of the international search	Date of mailing of the international search report
3 May 1995	19.05.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/EP 95/00193

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-443132	28-08-91	AU-B-	640185	19-08-93
		AU-A-	6801090	27-06-91
		CN-A-	1064080	02-09-92
		DE-D-	69005286	27-01-94
		DE-T-	69005286	21-04-94
		ES-T-	2060910	01-12-94
		FI-B-	93548	13-01-95
		JP-A-	4210996	03-08-92
EP-A-394989	31-10-90	AT-T-	115961	15-01-95
		DE-D-	69015244	02-02-95
		JP-A-	3027399	05-02-91
		US-A-	5164372	17-11-92
WO-A-9413694	23-06-94	AU-B-	5650894	04-07-94

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/EP 95/00193

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
CLAIMS SEARCHED INCOMPLETELY : 1 - 4
CLAIMS NOT SEACHED : 12-14

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP95/00193

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

The vast number of theoratically conceivable compounds resulving from the general formula (I) with it's broadly defined substitments predudes a comprehensive search. In accordance with the single example and guided by the concept of the invention as inferred from the list of compounds what can be drained, the search was limited to the general formula (I) wherein :

Y = 3-indolyl or a possibly substituted phenyle
B = CH
A = CH, O or N
X1= -CONR8-
X2= -CONR8-
n = 1

Concerning the intermediates (claims 12-14)- of which claim 13 can hardly be searched at all-these have not been searched "per se" because of the novelty of the end-products and for reasons of economy of the search. (cf.Arts. 6, 15 and rule 33 PCT ; see guidelines B-III 2.1)